Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Streptococcus pneumoniae is an important cause of otitis media, meningitis, bacterermia, and pneumonia, and a leading cause of fatal infections in the elderly and persons with underlying medical conditions, such as pulmonary disease, liver disease, alcoholism, sickle cell anemia, cerebrospinal fluid leaks, acquired immune deficiency syndrome (AIDS), and patients undergoing immunosuppressive therapy. It is also a leading cause of morbidity in young children. Pneumococcal infections cause approximately 40,000 deaths in the U.S. each year. The most severe pneumococcal infections involve invasive meningitis and bacteremia infections, of which there are 3,000 and 50,000 cases annually, respectively.

Despite the use of antibiotics and vaccines, the prevalence of pneumococcal infections has declined little over the last twenty-five years; the case-fatality rate for bacteremia is reported to be 15-20% in the general population, 30-40% in the elderly, and 36% in inner-city African Americans. Less severe forms of pneumococcal disease are pneumonia, of which there are 500,000 cases annually in the U.S., and otitis media in children, of which there are an estimated 7,000,000 of such cases each year that are caused by pneumococcus. Strains of drug-resistant *S. pneumoniae* are becoming ever more common in the U.S. and worldwide. In some areas, as many as 30% of pneumococcal isolates are resistant to penicillin. The increase in antimicrobial resistant pneumococcus further emphasizes the need for preventing pneumococcal infections.

S. pneumoniae asymptomatically colonizes the upper respiratory tract of normal individuals; the disease often results from the spread of organisms from the nasopharynx to other tissues during opportunistic events. The incidence of carriage in humans varies with age and circumstances. Carrier rates in children are typically higher than those of adults. Studies have demonstrated that 38 to 60% of preschool children, 29 to 35% of grammar school children, and 9 to 25% of junior high school children are carriers of the bacterium. Among adults, the rate of carriage drops to 6% for those without children at home, and to 18 to 29% for those with children at home. It is not surprising that the higher rate of carriage in children than in adults parallels the incidence of pneumococcal disease in these populations.

A goal for streptococcal vaccination is to reduce carriage in the vaccinated populations, and subsequently reduce the incidence of pneumococcal disease. There is

speculation that a reduction in pneumococcal carriage rates by vaccination could reduce the incidence of the disease in non-vaccinated individuals as well as vaccinated individuals. This "herd immunity" induced by vaccination against upper respiratory bacterial pathogens has been observed using the *Haemophilus influenzae* type b conjugate vaccines.

It is generally accepted that immunity to *S. pneumoniae* can be mediated by specific antibodies against the polysaccharide capsule of the bacterium. However, neonates and young children fail to make adequate immune response against most capsular polysaccharide antigens and can have repeated infections involving the same capsular serotype. One approach to immunizing infants against a number of encapsulated bacteria is to conjugate the capsular polysaccharide antigens to a protein to make them immunogenic. This approach has been successful, for example, with *H. influenzae* type b.

However, there are over ninety known capsular serotypes of S. *pneumoniae,* of which twenty-three account for about 95% of the disease. For a *S. pneumoniae* polysaccharide-protein conjugate to be successful, each of the capsular types responsible for most pneumococcal infections would have to be made adequately immunogenic. This approach may be difficult, because the twenty-three polysaccharides included in the presently-available vaccine are not all adequately immunogenic, even in adults.

Protection mediated by anti-capsular polysaccharide antibody responses are restricted to the polysaccharide type. Different polysaccharide types differentially facilitate virulence in humans and other species. Pneumococcal vaccines have been developed by combining 23 different capsular polysaccharides that are the prevalent types of human pneumococcal disease. These 23 polysaccharide types have been used in a licensed pneumococcal vaccine since 1983. The licensed 23-valent polysaccharide vaccine has a reported efficacy of approximately 60% in preventing bacteremia caused by vaccine type *S. pneumoniae* in healthy adults.

However, the efficacy of the vaccine has been controversial, and at times, the justification for the recommended use of the vaccine questioned. It has been speculated that the efficacy of this vaccine is negatively affected by having to combine 23 different antigens. Having a large number of antigens combined in a single formulation may negatively affect the antibody responses to individual types within this mixture because of antigenic competition. The efficacy is also affected by the fact that the 23 serotypes do not encompass all serological types associated with human infections and carriage.

An alternative approach for protecting children, and also the elderly, from *S. pneumoniae* infection would be to identify protein antigens that elicits protective immune responses. Such proteins may serve as vaccines by themselves, may be used in conjunction with polysaccharide-protein conjugates, or as carriers for polysaccharides.

McDaniel et al., *J. Exp. Med.*, 160:386-397 (1984) relates to the production of monoclonal antibodies that recognize cell surface polypeptide(s) on *S. pneumoniae* and protection of mice from infection with certain strains of encapsulated *S. pneumoniae* by passive immunization with such antibodies. This surface protein antigen has been termed "pneumococcal surface protein A", or "PspA" for short. PspA has been identified as a virulence factor and a protective antigen. PspA is a cell surface molecule that is found on all clinical isolates, and the expression of PspA is required for the full virulence of *S. pneumoniae* in mouse models. The biological function of PspA has not been well defined, although a preliminary report suggests that it may inhibit complement activation.

McDaniel et al., *Microbial Pathogenesis*, 1:519-531 (1986) relates to studies on the characterization of the PspA. Considerable diversity in the PspA molecule in different strains was found, as were differences in the epitopes recognized by different antibodies. McDaniel et al., *J. Exp. Med.*, 165:381-394 (1987) relates to immunization of X-linked immunodeficient (XID) mice with non-encapsulated *S. pneumoniae* expressing PspA, which protects mice from subsequent fatal infection with *S. pneumoniae*. Immunization with isogenic *S. pneumoniae* which did not express PspA did not confer protection. McDaniel et al., *Infect. Immun.*, 59:222-228 (1991) relates to immunization of mice with a recombinant PspA that is able to elicit protection against *S. pneumoniae* strains of capsular types 6A and 3. Crain et al., *Infect. Immun.*, 56:3293-3299 (1990) relates to a rabbit antiserum that detects PspA in 100% (n = 95) of clinical and laboratory isolates of strains of *S. pneumoniae*. When reacted with seven monoclonal antibodies to PspA, fifty-seven *S. pneumoniae* isolates exhibited thirty-one different patterns of reactivity.

The PspA protein type is independent of capsular type. Serological analysis of PspA using a panel of seven monoclonal antibodies indicated that, like capsular polysaccharides, the PspA molecules are highly diverse among pneumococcal strains. Based on these analyses, over 30 PspA protein serotypes were defined and individual strains were assigned into groups, i.e., families (or serotypes) using a classification system based upon reactivity with the panel of monoclonal antibodies. Moreover, SDS-PAGE analysis indicated that, within a PspA serotype, further heterogeneity existed on the basis of the molecular size.

This diversification further supports the assertion that PspA is a protective antigen in natural infections; the protective nature of anti-PspA responses has presumably applied selective pressure on pneumococcus to diversify this molecule.

Immunization with PspA in a lysate of a recombinant λgtl1 clone is reported to elicit protection against challenge with several *S. pneumoniae* strains representing different capsular and PspA types. Although clones expressing PspA were constructed, the product was insoluble and isolation from cell fragments following lysis was not possible.

Analysis of the nucleotide and amino acid sequences of the PspA molecule reveals three major regions. The first 288 amino acids at the amino terminal end of the protein are predicted to have a strong alpha helical structure. The adjacent region of 90 amino acids (289 to 369 of Rx1 PspA) has a high density of proline residues. The remaining 196 amino acids at the carboxyl-terminal end of the molecule (370 to 588 of Rx1 PspA) have a repeated amino acid sequence that has been demonstrated to bind to phosphocholine and lipoteichoic acids. Based on this structure, the PspA molecule is thought to associate with the inner membrane and lipoteichoic acids via the repeated region in the middle of the carboxyl-terminal end of the protein. The proline region in the middle of the protein is thought to traverse the cell wall, placing the alpha helical region on the outer surface of the *S. pneumoniae* cells. This model is consistent with the demonstration that the alpha helical region, which extends from the surface of the cell, contains the protective epitopes.

U.S. Patent No. 5,476,929 relates to vaccines comprising PspA and fragments thereof, DNA encoding PspA and fragments thereof, methods for expressing DNA encoding PspA and fragments thereof, the amino acid sequences of PspA and fragments thereof, compositions containing PspA and fragments thereof, and methods of using such compositions.

Alternative vaccination strategies are desirable as they provide alternative routes to administration or alternative routes to generation of immune responses. The prior art fails to provide broadly efficacious *S. pneumoniae* vaccines. It would be advantageous to provide an immunological composition or vaccination regimen which elicits protection against various diverse *S. pneumoniae* strains, without having to combine a large number of possibly immunocompetitive or interfering antigens within the same formulation. By allowing a rational selection of representative PspAs from the various families of clades, broadly efficacious vaccines can be produced.

The present invention is directed to achieving these objectives.

In response to item 3 on page 2 of the outstanding office action, paragraph **[0001]** of the specification has been amended to update the status of the applications in the priority statement.

The objection to the specification is obviated in view of the above amendments.

The rejection of claims 1-34 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

Claim 1 has been amended to recite "[a] vaccine or immunogenic composition comprising at least an isolated PspA and an isolated immunogenic fragment of PspA from *S. pneumoniae* strains from at least two PspA families...." Applicants submit that this amendment to claim 1 makes it clear that the claimed composition contains at least an isolated PspA from one PspA family and an isolated immunogenic fragment of PspA from another PspA family. Since those skilled in the art would fully understand what is meant by the amended claims, the meaning of the claims is not indefinite. Thus, the rejection under 35 U.S.C. §112 (2nd para.) should be withdrawn.

The rejection of claims 1 and 2 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 6,638,516 is respectfully traversed in view of the attached terminal disclaimer.

The rejection of claims 1 and 2 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,955,089 is respectfully traversed in view of the attached terminal disclaimer.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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Ruth R. Smith